INTERIM REPORT - UPPER OTTAWA STREET LANDFILL SITE STUDY, REFERENCE PAPER 24 : TOXICITY PROFILE FOR CHEMICALS

REFERENCE 24

Toxicity Profile
FOR
CHEMICALS

TOXICITY PROFILE

FOR

ACRYLIC ACID

PREPARED FOR:

UPPER OTTAWA STREET
LANDFILL STUDY
SUITE 33
42 JAMES STREET SOUTH
HAMILTON, ONTARIO, CANADA
L8P 2Y4

PREPARED BY:

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January 28, 1983

TOXICITY PROFILE FOR CHEMICALS

1. CHEMICAL NAME: Acrylic acid

2. CAS NUMBER: 79-10-7

3. SYNONYMS/TRADE NAMES: acroleic acid; acrylic acid (DOT); acrylic acid (glacial); ethylene carboxylic acid; propene acid; propenioc acid, vinylformic acid.

4. CHEMICAL/PHYSICAL PROPERTIES:

Description	Colorless, fuming, corrosive liquid with an acrid odor
Boiling Point	141.6C
Melting Point	13.0C
Molecular Formula	$C_3H_4O_2$
Reactivity	The glacial acid corrodes iron and steel
Molecular Weight	72.1
Solubility	Miscible with water, ether & ethanol; moderately soluble in acetone and benzene
Vapour Density	2.5
Vapour Pressure	52 mm Hg @ 20C

5. SOURCES/USES:

Occurs natrually in marine algae, in the rumen fluid of sheep and in commercial grade propionic acid. Has been identified as an air contaminant;

Mostly manufactured by 1) oxidation of propylene, 2) hydrolysis of acrylonitrile and acrylamide and conversion to acrylic acid.

In 1976, 70 million kG was produced in the U.S., about 150 million kG in the European Community;

Approximately 80% of acrylic acid produced is used captively as a precursor of acrylates, the remainder is used in the production of water soluble resins and salts, as a co-monomer in acrylic emulsion and solution polymers and in the production of special acrylates. About 50% of acrylates are used in surface coatings, 23% in textile applications and remainder in the production of paper, polishes, acrylic fibres, leather and miscellaneous applications (for further details on the production and use of acrylic acid, refer to the IARC (1979);

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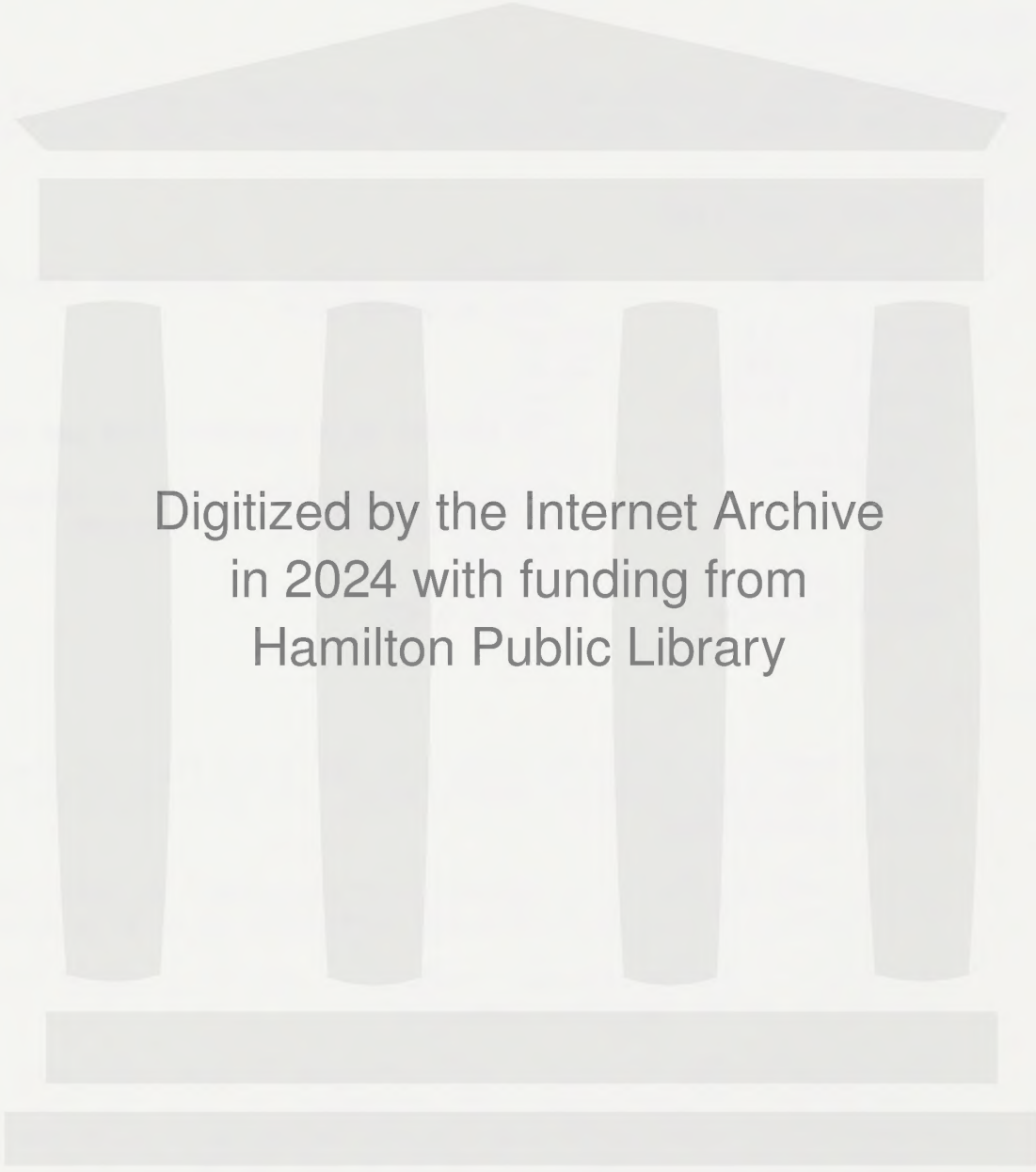

6. REGULATORY INFORMATION/EXPOSURE LIMITS/ETC.:

TLV - 10ppm recommended at the American Conference of Governmental Industrial Hygienists in 1980 (Miller et al (1981)

7. GENERAL TOXICITY INDICES: (Definitions of the descriptions of exposures used in this toxicity profile are given in Appendix I, page 7 & 8)

MICE - LD_{50} (oral) = 830 mG/kG body weight (Klimkina et al, 1969).

Rats - LD_{50} (i.p. injection) = 24 mG/kG (Majka et al, 1974; IARC, 1979).

LD_{50} (oral) = 193 to 350 mG/kG body weight for glacial acrylic acid and 2100 to 3200 mG/kG body weight for acrylic acid (Klimkina et al, 1969, IARC, 1979). Carpenter et al (1974) reported a value of 390 mG/kG for acrylic acid.

LD_{50} (oral) = 2.59 mL glacial acrylic acid/kG body weight (Smith et al, 1962)

LC_{50} (inhal for 4 hours) = 3600 mG/M^3 or 1200 ppm (Majka et al, 1974).

Saturated vapour concentrations killed half of a group of test rats in 3.5 hours (IARC, 1979).

Rabbits - LD_{50} (oral) = 250 mG/kG (Klimkina et al, 1969)

LD_{50} (skin) = 295 to 750 mG/kG body weight (IARC, 1979); 0.95 mL/kG (Smith et al, 1962 and Miller et al, 1981)

Primary Skin Irritation = 0.01 mL glacial acrylic acid applied directly to shaven skin produced necrosis in 24 hours (Smith et al, 1962)

Eye Irritation (Draize test) = server burns produced within 24 hours of application of 0.005 mL glacial acrylic acid directly to the eye (Smith et al, 1962)

8. GENERAL SYMPTOMS/SIGNS OF EXPOSURE:

Mice - Pronounced growth retardation and nasal lesions after inhalation exposure (6 hr/day for 2 weeks) to 250 ppm (Miller et al, 1981).

Altered conditioned reflex activities after exposure to 25 mG/kG for 3 months (Klimkina et al, 1969).

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12 weeks exposure to 25 or 75 ppm for 6 hours per day resulted in a significantly decreased in body weight gain of female mice but had no effects on organ weights, hematology, clinical chemistry or urinalysis parameters. Male mice were not affected. Some mice at 75 ppm had histopathologic lesions in the olfactory epithelium (but not the respiratory epithelium) of the nasal mucosa consisting of degeneration and inflammatory cell infiltration of the olfactory mucosa. In some mice there was hyperplasia of the submucosal glands and replacement of the olfactory epithelium by respiratory epithelium. These effects were attributed to irritation from acrylic acid (Miller et al, 1981)

Rats - Strong local irritation leading to irreversible changes in skin & eyes on exposure to vapours in air (IARC, 1979).

5 weeks exposure to acrylic acid vapours at 700 mG/M^3 (240 ppm) for 4 hours per day resulted in decreased body weight gains and increased numbers of blood erythrocytes (Majka et al, 1974).

Single and repeated doses of 1500 or 300 ppm resulted in nasal irritation, lethargy and reduced body weight gain. 80 ppm had no effect (Gage, 1970).

Pronounced growth retardation and nasal lesions after inhalation exposure (6 hr/day for 2 weeks) to 250 ppm (Miller et al, 1981).

238 ppm for 4 hr/day fo 5 weeks caused increased urinary excretion of phenol red, decreased urine concentration ability and increased numbers of erythrocytes, lesions of the gastric mucosa and inflammation of the upper respiratory tract (Majka et al, 1974).

12 weeks exposure to 5, 25 or 75 ppm for 6 hours per day had no effects on body weights, body weight gains, organ weights, hematologic, clinical chemistry or urinalysis parameters. Rats at 75 ppm had histopathologic lesions in the olfactory epithelium (but not the respiratory epithelium) of the nasal mucosa consisting of degeneration and inflammatory cell infiltration of the olfactory mucosa. These effects were attributed to irritation from acrylic acid (Miller et al, 1981)

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Rabbits - Severe irritation and corneal burns when applied to the eyes. Did not produce sensitization in the Draize test (Magnusson et al , 1969)

6 months exposure to 2.5 mG/kG resulted in altered carbohydrate and protein synthesis functions in the liver, increased blood chloride levels and degenerative lesions in the stomach, intestines, kidney, adrenals, liver, pancrease, spleen and central nervous system (Klimkina et al, 1969).

Guinea Pigs - Acrylic acid is a definite sensitizer by the guinea pig maximization test (Magnusson et al , 1969)

Humans - Acrylic acid is an irritant of the upper respiratory tract, eyes and gastro-intestinal tract in occupational settings. No definitive toxicology is available in humans.

9. CARCINOGENICITY/MUTAGENICITY:

No data on carcinogenicity or mutagenicity of acrylic acid were available (IARC, 1979).

10. REPRODUCTIVE EFFECTS/TERATOGENICITY:

Studies in rats indicated significant increases in the numbers of gross abnormalities following treatment with 4.7 or 8.0 mG/kG body weight (given on days 5, 10 & 15 of gestation). Skeletal abnormalities were significantly increased in offspring from females treated with 8.0 mG/kG. Embryotoxicity was observed at the highest dose level (Singh et al, 1972).

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11. APPRAISAL OF POTENTIAL HAZARD FROM ACRYLIC ACID ASSOCIATED WITH THE UPPER OTTAWA STREET LANDFILL SITE:

The toxicology of acrylic acid has not been studied as extensively as the various acrylate esters, primarily because acrylic acid is normally used under captive conditions and direct exposures are less likely. Generally, the types of toxicological responses reported in comparative studies between acrylic acid and acrylate esters are similar, i.e. irritant effects in the upper respiratory tract, histopathological lesions in the epithelial structures of the respiratory tract, lesions of the gastro-intestinal tract at high dosages, embroytoxicity and gross teratologic abnormalities and possible immune sensitization. The major difference in the toxicology is that acrylic acid is somewhat more toxic than are the acrylate esters (the toxic potencies are only slightly different, except for reproductive effects where acrylic acid is about 50 time more toxic that its esters).

Considering that responses are similar where comparable data are available, data from acrylate esters could be used to identify potential health threats in areas where data are lacking for acrylic acid per se. The toxicology data available on various acrylate esters has been summarized by Autian (1975). The apparent rapid metabolism and elimination of acrylate esters suggests that these monomers should not be cumulative toxins and both animal bioassays and human experience from long-term monitoring of industrial environments demonstrates that these agents are not carcinogenic (Autian, 1975). The data supports the contention that acrylate esters have a very low order of toxicity but caution is indicated in serveral areas:

- the potential sensitizing activity indicates caution in population groups particularly prone to "allergic-type" responses;

- effects on the cardiovascular system (increased blood pressure, heart rate and respiration rate) may indicate a greater risk to those predisposed to cardiovascular disease;

- embryotoxic and teratogenic effects suggest that pregnant women may be a high risk group, although the doses require to produce these effects in experimental animals were high;

Assuming that the similarity with acrylate esters holds true, the high risk population groups for acrylic acid would include those predisposed to "allergic-type" reactions, those with cardiovascular disease and pregnant women. Due to the greater potency of acrylic acid as a reproductive toxin, pregnant women would warrent greater attention than than other groups.

Analytical information indicates that the maximum acrylic acid concentrations at the Upper Ottawa Landfill Site was 4.72 ppb (or 4.92 uG/L; Sciex, 1982, TABLE 4.2-2, page 16). Assuming that the average 50 kG human breaths 20 L of air /day containing 4.72 ppb acrylic acid and that 100% of the acrylic acid is absorbed into the body, the intake of acrylic acid would be 98.4 ug/50 kG person/day. The lowest acute dose of acrylic acid shown to cause toxic effects in experimental animals is 5 mG acrylic acid/kG. Assuming equivalent responses between experimental animals and humans (an assumption by no means proven), the data indicates that the acute effect dose for humans would be 250 mG of acrylic acid which is over 2500 times lower than the calculated intake of acrylic acid given above.

Another approach to obtaining a crude estimate of the hazard posed to residents near the landfill site is to compare the levels of acrylic acid found in air from the landfill site with the Threshold Limit Values proposed at the ACGIH (Miller et al, 1981) of 10 ppm in the atmosphere of the work environment. Assuming direct proportionality with time, this would be equivalent to about 3.3 ppm in the home environment where exposure could be on a 24 hour/day basis rather than 8 hours/day. Since the available evidence indicates that acrylic acid is primarily an acute rather than a chronic toxin, this assumption may be reasonable. Based on these assumptions, the levels of acrylic acid measured in air from vents on the landfill site was about 670 times lower than the TLV proposed for the work environment.

Even though acrylic acid may be more toxic than the acrylate esters, the threat to human health from the levels reported at the landfill site must be considered minimal. However, such a statement requires confirmation by a comprehensive assessment of the health of those residing near the landfill site. With respect to acrylic acid, such an assessment should evaluate the high risk population groups indicated above, in particular pregnant women, those with cardiovascular disease and individuals sensitive to allergenic agents.

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12. REFERENCE MATERIAL:

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Carpenter, C.P., C.S. Weil and H.F. Smyth. 1974. Range-finding toxicity data: List VIII. Toxicol. Appl. Pharmacol. 28:313-319.

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Miller,, R.R., J.A. Ayres, G.C. Jersey and M.J. McKenna. 1981. Inhalation toxicity of acrylic acid. Fundamental Appl. Toxicol. 1:271-277.

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Sciex, 1982. Draft Report. Air quality surveys of Upper Ottawa Street Landfill Study. Prepared for Upper Ottawa Street Landfill Study, Suite 33, 42 James Street South, Hamilton, Ontario, L8P 2Y4.

Singh, A.R., W.H. Lawrence and J. Autian. 1972. Embryonic-fetal toxicity and teratogenic effects of a group of methylacrylate esters in rats. J. Dental Res. 51:1632

Smith, H.F., C.P. Carpenter, C.S. Weil, U.C Pozzani and J.A. Striegel. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-107.

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APPENDIX I: DESCRIPTION OF EXPOSURE:

The following abbreviations, adopted from NIOSH (1979), were used to describe the dosage of the chemical in this toxicity profile;

TD_{lo} = Toxic Dose Low = the lowest dose of a substance introduced by any route other than inhalation over any given period of time and reported to produce any toxic effect in man or to produce carcinogenic, teratogenic, mutagenic or neoplastic effects in humans or animals.

TC_{lo} = Toxic Concentration Low = any concentration of a substance in air to which man or animals have been exposed for any given period of time and that has been reported to produce any toxic effect in man, or to produce a carcinogenic, teratogenic, mutagenic or neoplastic toxic effect in animals or humans.

LD_{lo} = Lethal Dose Low = the lowest dose of a substance, other than LD_{50}, introduced by any route other than inhalation over any given period of time and reported to have caused death in man or the lowest single dose introduced in one or more divided portions and reported to have caused death in animals.

LD_{50} = Lethal Dose Fifty = a calculated dose of a chemical substance which is expected to cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance, by any route other than inhalation, of a significant number from that population. Other lethal dose percentages, such as LD_1, LD_{10}, LD_{20}, LD_{99} etc. may also be given if available.

LC_{lo} = Lethal Concentration Low = the lowest concentration of a substance, other than an LC_{50}, in air which has been reported to have caused death in man or to have caused death in animals when they have been esposed for 24 hours or less.

LC_{50} = Lethal Concentration Fifty = a calculated concentration of a substance in air, exposure to which for 24 hours or less would cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance of a significant number from that population.

The following abbreviations were used to describe the route of administration of the substance:

Oral = administered via the mouth

Dermal = applied to the skin

ip = interperitoneally

iv = intravenously

Subcut. = injected subcutaneously

Inh = inhalation

TOXICITY PROFILE

FOR

CRESOL

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TOXICITY PROFILE FOR CHEMICALS

NOTE: There are 3 isomers of cresol; m-cresol (A - page 2)
o-cresol (B - " 4)
p-cresol (C - " 7)

The letters m-, o- and p- preceeding the chemical name denote the relative positions of the methyl groups to the hydroxyl groups on the benzene rings and the information in brackets following each isomer denotes the section and page number of this toxicity profile where the available data for that isomer is presented. All cresol isomers are consider together in Section 8 (page 9) on the overall appraisal of the potential health threat from cresol associated with the Upper Ottawa Street Landfill Site.

All isomers have similar descriptive characteristics, appearing as a colorless to yellowish to brownish-yellow liquid with a phenolic, sweet, tarry odor that becomes darker with age or on exposure to light. Most commercial sources are mixtures of the three isomer, in which the m-cresol predominates. Isomeric mixtures may be known as cresylic acid, cresylol or tricresol. They are the major constituent of "cresylic acid". Cresols are soluable in 50 parts water, miscible with alcohol, ether, benzene, petroleum ether and in NaOH solutions.

Cresols are obtained from coal tar and usually contain a few percent phenol. They can be prepared by sulfonation of toluene or the oxidation of toluene. Cresols are used in the preparation of synthetic resins, in photographic developers and explosives and as disinfectants, local antiseptics, fungicides and parasitides.

An upper limit level for workroom air of 5 ppm is recommended (American Conference of Government and Industrial Hygienists, 1971) to prevent any serious degree of irritation from cresol vapours. It is generally agreed that cresol is not volatile enougn to constitute a respiratory hazard under normal conditions but that is can act as a strong irritant on direct contact and cause frequent dermititis. Poisoning has been reported when large areas of the skin were exposed to cresol and not removed immediately. General symptoms and signs of chronic poisoning from oral or dermal absorption include digestive disturbances, nervous disorders, skin eruptions, jaundice, oliguria and uremia. Cresol is considered a general protoplasmic poison.

CRESOL..../2

1A. CHEMICAL NAME: m-cresol

2A. CAS NUMBER: 108-39-4

3A. SYNONYMS/TRADE NAMES: 3-cresol, m-cresylic acid, 1-hydroxyl-3-methylbenzene, m-hydroxytoluene, m-kresol, m-methylphenol, 3-methylphenol, m-oxytoluene

4A. CHEMICAL/PHYSICAL PROPERTIES:

Boiling point	202.8C
Melting point	12C
Molecular Weight	108.15
Molecular Formula	C_7H_8O
Specific gravity	1.034
Vapour density	3.72
Vapour pressure	1 mm Hg @ 25C

5A. GENERAL TOXICITY INDICES: (Definitions of the descriptions of exposures used in this toxicity profile are given in Appendix I, page 15)

FROG - LD_{10} (subcut.) = 250 mG cresol/kg body weight (NIOSH, 1979)

MICE - LD_{50} (oral) = 828 mG cresol/kG body weight (NIOSH, 1979).

LD_{50} (ip) = 168 mG cresol/kG body weight (NIOSH, 1979)

LD_{50} (subcut.) = 450 mG cresol/kG body weight (NISOH, 1979)

TD_{10} (skin) = 2280* mG cresol/kG body weight (20% solution applied twice weekly) over a 12 week time period resulted in 50% skin papillomas and 0% carcinomas (Original study by Boutwell and Bosch, 1959, assessed by Schubik and Hartwell, 1972-73, NIOSH, 1979 and Sax, 1981).

RAT - LD_{50} (oral) = 242 mG cresol/kG body weight (NIOSH, 1979)

LD_{50} (subcut.) = 900 mG cresol/kG body weight (NIOSH, 1979)

LD_{50} (dermal) = 620 mG cresol/kG body weight (NIOSH, 1979)

* Calculation of dosage in skin application studies presented in Section 8, page 9 of this toxicity profile

CRESOL..../3

RABBIT - Primary irritation dose (skin) = 517 mG cresol/kG body weight (severe reaction) (NIOSH, 1979)

Primary irritation dose (eye, Draize test) = 103 mG cresol/kG body weight (severe reaction) (NIOSH, 1979)

LD_{50} (oral) = 1400 mG cresol/kG body weight (NIOSH, 1979)

LD_{50} (dermal) = 2050 mG cresol/kG body weight (NIOSH, 1979)
= 2830 mG cresol/kG body weight (Vernot et el, 1977)

LD_{50} (subcut.) = 500 mG cresol/kG body weight (NIOSH, 1979)

LD_{50} (iv) = 280 mG cresol/kG body weight (NIOSH, 1979)

GUINEA PIG - LD_{10} (subcut.) = 300 Mg cresol/kG body weight (NIOSH, 1979)

LD_{10} (ip) = 100 mG cresol/kG body weight (NIOSH, 1979)

DOG - LD_{20} (iv) = 150 mG cresol/kG body weight (NIOSH, 1979)

CAT - LD_{10} (subcut.) = 180 mG cresol/kG body weight (NIOSH, 1979)

HUMAN - LD (probable) = 50 - 500 mG cresol (Handbook of Toxicology, 1959)

6A. GENERAL SYMPTOMS/SIGNS OF EXPOSURE:

RABBIT - Dermal and mucous membrane irritation studies indicate m-cresol is a strong irritant, generally considered somewhat greater than phenol (American Conference of Government and Industrial Hygienists, 1971). Systemic toxicity of m-cresol is less than phenol (Handbook of Toxicology, 1979)

HUMAN - The low volatility of cresol reduces the respiratory hazard under normal conditions in occupational settings but skin irritation, dermatitis and skin burns can be caused by direct contact. The general effects of m-cresol are indistinquishable from the isomeric mixture; m-cresol is the least potent isomer of the three. Its toxic action is approximately the same as phenol; slightly more corrosive but milder in systemic effects.

CRESOL..../4

7A CARCINOGENICITY/MUTAGENICITY:

MICE - Shown to promote carcinogenicity of the initiating agent, 9,10-dimethyl-1,2- benzanthracene (DMBA). Incidence of skin papillomas after 12 weeks treatment = 50% compared to 0% in mice treated with DMBA alone. Incidence of carcinomas in survivors was 0% at 12 weeks (Boutwell and Bosch, 1959). Cresol was not tested for carcinognicity without an initiating agent (Boutwell and Bosch, 1959). There are no significant differences between the various cresol isomers with respect to the production of skin papillomas in mice (Boutwell and Bosch, 1959).

HUMAN - Cresol is classed as a dermal contact carcinogen (NIOSH, 1979 and Sax, 1981).

1B. CHEMICAL NAME: o-cresol

2B. CAS NUMBER: 95-48-7

3B. SYNONYMS/TRADE NAMES: 2-cresol, o-cresylic acid, orthocresol, 1-hydroxy-2-methylbenzene, o-hydroxytoluene, o-methylphenol, 2-methylphenol, o-oxytoluene

4B. CHEMICAL/PHYSICAL PROPERTIES:

Boiling point	191C
Melting point	31C
Molecular Weight	108.15
Molecular Formula	C_7H_8O
Specific gravity	1.05
Solubility in water	2.5%
Vapour density	3.72
Vapour pressure	0.25 mm Hg @ 25C

5B. GENERAL TOXICITY INDICES:

FROG - LD_{10} (subcut.) = 200 mG cresol/kG body weight (NIOSH, 1979)

CRESOL..../5

MICE - LD_{50} (oral) = 344 mG cresol/kG body weight (NIOSH, 1979)

LD_{10} (subcut.) = 410 kG cresol/kG body weight (NIOSH, 1979).

TD_{10} (skin) = 4800* mG cresol/kG body weight (20% solution applied twice weekly) over a 12 week time period following pretreatment with DMBA as an initiator resulted in 59% skin papillomas and 0% carcinomas (Original study by Boutwell and Bosch, 1959, assessed by Schubik and Hartwell, 1972-73, NIOSH, 1979 and Sax, 1981).

Rats - LD_{50} (oral) = 121 mG cresol/kG body weight (NIOSH, 1979)

LD_{50} (dermal) = 1110 mG cresol/kG body weight (NIOSH, 1979)

RABBIT - Primary irritation dose (skin) = 524 mG cresol/24 hr (severe effect) (NIOSH, 1979)

Primary irritation dose (eye, Draize test) = 105 mG cresol (severe effect) (NIOSH, 1979)

LD_{50} (dermal) = 890 mG cresol/kG body weight (NIOSH, 1979)
= 700 to 5900 mG cresol/kG body weight (Vernot et al, 1977)

LD_{10} (oral) = 940 mg cresol/kG body weight (NIOSH, 1979)

LD_{10} (subcut.) = 450 mG cresol/kG body weight (NIOSH, 1979)

LD_{10} (iv) = 180 mg cresol/kG body weight (NIOSH, 1979)

GUINEA PIG - LD_{10} (ip) = 360 mG cresol/kG body weight (NIOSH, 1979)

DOG - LD_{10} (iv) = 80 mG cresol/kG body weight (NIOSH, 1979)

CAT - LD_{10} (subcut.) = 55 mG cresol.kG body weight (NIOSH, 1979)

CRESOL..../6

6B. GENERAL SYMPTOMS/SIGNS OF EXPOSURE:

RABBIT - Dermal and mucous membrane irritation studies indicate o-cresol is a strong irritant, generally considered somewhat greater than phenol (American Conference of Government and Industrial Hygienists, 1971). Systemic toxicity of o-cresol is less than phenol (Handbook of Toxicology, 1979)

HUMAN - The low volatility of cresol reduces the respiratory hazard under normal conditions in occupational settings but skin irritation, dermatitis and skin burns can be caused by direct contact. The general effects of o-cresol are indistinquishable from the isomeric mixture; o-cresol is more toxic than the m-isomer but less toxic than p-cresol. Its toxic action is similar to phenol; slightly more corrosive but milder in systemic effects.

7B. CARCINOGENICITY/MUTAGENICITY:

Mice - Shown to promote carcinogenicity of the initiating agent, 9,10-dimethyl-1,2- benzanthracene (DMBA). Incidence of skin papillomas after 15 weeks treatment = 59% compared to 0% in mice treated with DMBA alone. Incidence of carcinomas in survivors was 18% at 23 weeks (Boutwell and Bosch, 1959). Cresol was not tested for carcinognicity without an initiating agent (Boutwell and Bosch, 1959). There are no significant differences between the various cresol isomers with respect to the production of skin papillomas in mice (Boutwell and Bosch, 1959).

HUMAN - Cresol is classed as a dermal contact carcinogen (NIOSH, 1979 and Sax, 1981).

* Calculation of dosage in skin application studies presented in Section 8, page 9 of this toxicity profile

1C. CHEMICAL NAME: p-cresol

2C. CAS NUMBER: 106-44-5

3C. SYNONYMS/TRADE NAMES: 4-cresol, p-cresylic acid, 1-hydroxy-4-methylbenzene, p-methylphenol, p-hydroxytoluene, 4-hydroxytoluene, 4-Kresol, 1-methyl-4-hydroxybenzene, 4-methylphenol, p-oxytoluene, para-cresol, paramethylphenol.

4C. CHEMICAL/PHYSICAL PROPERTIES:

Boiling point	201.9C
Melting point	28-32C
Molecular Weight	108.13
Molecular Formula	C_7H_8O
Specific gravity	1.0347
Solubility in water	slight

5C. GENERAL TOXICITY INDICES:

FROG - LD_{10} (subcut.) = 150 mG cresol/kG body weight (NIOSH, 1979)

MICE - LD_{50} (oral) = 344 mG cresol/kG body weight (NIOSH, 1979)

LD_{50} (ip) = 25 mG cresol/kG body weight (NIOSH, 1979)

LD_{10} (subcut.) = 150 mG cresol/kG body weight (NIOSH, 1979)

TD_{10} (skin) = 4800* mG cresol/kG body weight (20% solution applied twice weekly) over a 12 week time period resulted in 35% papillomas and 0% carcinoma (orginal study by Boutwell and Bosch, 1959; assessed by Schubik and Hartwell, 1972-73; NIOSH, 1979 and Sax, 1981)

RATS - LD_{50} (oral) = 207 mG cresol/kG body weight (NIOSH, 1979)

LD_{50} (dermal) = 750 mG cresol/kG body weight (NIOSH, 1979)

LD_{10} (subcut.) = 500 mG cresol/kG body weight (NIOSH, 1979)

GUINEA PIG - LD_{10} (subcut.) = 200 mG cresol/kG body weight (NIOSH, 1979)

* Calculation of dosage in skin application studies presented in Section 8, page 9 of this toxicity profile

CRESOL..../8

RABBITS - Primary irritation dose (skin) = 517 mG cresol/24 hr. (severe effect) (NIOSH, 1979)

Primary irritation dose (eye, Draize test) = 103 mG cresol

LD_{10} (oral) = 620 mG cresol/kG body weight (NIOSH, 1979)

LD_{50} (dermal) = 301 mG cresol/kG body weight (NIOSH, 1979)
= 130 to 910 mG cresol/kG body weight (Vernot et al, 1977)

LD_{10} (subcut.) = 300 mG cresol/kG body weight (NIOSH, 19790

LD_{10} (iv) = 180 mG cresol/kG body weight (NIOSH, 1979)

CAT - LD_{10} (subcut.) = 80 mG cresol/kG body weight (NIOSH, 1979)

6C. GENERAL SYMPTOMS/SIGNS OF EXPOSURE:

RABBIT - Dermal and mucous membrane irritation studies indicate p-cresol is a strong irritant, generally considered somewhat greater than phenol (American Conference of Government and Industrial Hygienists, 1971). Systemic toxicity of p-cresol is less than phenol (Handbook of Toxicology, 1979)

HUMAN - The low volatility of cresol reduces the respiratory hazard under normal conditions but skin irritation, dermatitis and skin burns can be caused by direct contact. The general effects of p-cresol are indistinquishable from the isomeric mixture; p-cresol is more toxic than the m- or o- isomer. Its toxic action is similar to phenol; considerably more corrosive but milder in systemic effects.

7C. CARCINOGENICITY/MUTAGENICITY:

Mice - Shown to promote carcinogenicity of the initiating agent, 9,10-dimethyl-1,2- benzanthracene (DMBA). Incidence of skin papillomas after 15 weeks treatment = 35% compared to 0% in mice treated with DMBA alone. Incidence of carcinomas in survivors was 0% at 23 weeks (Boutwell and Bosch, 1959). p-Cresol was not tested for carcinognicity without an initiating agent (Boutwell and Bosch, 1959). There are no significant differences between the various creaol isomers with respect to the production of skin papillomas in mice (Boutwell and Bosch, 1959).

CRESOL..../9

HUMAN - Cresol is classed as a dermal contact carcinogen (NIOSH, 1979 and Sax, 1981).

8. APPRAISAL OF POTENTIAL HAZARD FROM CRESOL ASSOCIATED WITH THE UPPER OTTAWA STREET LANDFILL SITE:

The animal toxicity data on the various isomers of cresol focused primarily on carcinogenesis, acute toxicity and eye irritation. Toxicity data from human subjects exposed in occupational settings indicated that the cresol isomers are severe contact irritants. In this appraisal of the potential health threat related to cresol from the landfill site, carcinogenesis will be discussed first.

8.1. CARCINOGENESIS:

The available carcinogenicity data was collected from skin application studies in mice, usually designed to assess tumor promoting activity by pretreating the animals with DMBA. For the purpose of gaining some crude indication of risks to humans from such studies, the dosage of cresol was transposed from so many drops of a known percent solution of cresol per application to mG cresol/kG body weight/treatment period. The standard equation for this transposition was as follows:

$$\text{Total dose (D)} = \frac{d \times c \times f \times t}{W}$$

Where: d = volume of one drop (assumed to be 0.025 mL)
c = concentration of solution used (mG cresol/mL)
f = frequency of applications per week
t = number of weeks treatment
W = body weight of a mouse (assumed to be 0.025 kG)

(Similar calculations were made by Schubik and Hartwell, 1972-73 and NIOSH, 1979 in the assessment of the carcinogenicity data on cresol.)

It must be stressed that the process of extrapolating toxicity on carcinogenicity data from observations made on laboratory animals to the humans situation is far from exact. Questions of species differences in response to the agent, the possible differences in response induced by studying high dosages of the agent, lack of knowledge on the mechanism of action of most toxicants (particularly carcinogens) and the difficulties of extrapolating data outside the range of experimental observations to estimate levels of risks encountered in human populations, all contribute to the uncertainity of the process. Nevertheless, crude indications of the magnitude of hazard associated with exposure to a chemical agent can be gained from such assessments.

CRESOL..../10

The carcinogenicity studies with the cresols in mice involved skin application of the individual cresol isomers twice weekly for 12 weeks, preceeded by a single treatment with the initiating agent 9,10-dimethyl-1,2-benzanthracene (DMBA). Assuming equivalent sensitivity between mice and humans on a per kilogram body weight basis (an assumption by no means proven) and similar exposure conditions (including pre-treatment application of DMBA), the exposure level in humans required to produce skin tumors would be about 4800 mG cresol/kG body weight/12 weeks or about 2800 mG cresol/50 kG individual/day (assuming the average person weighs 50 kG).

The response relationship between different species of animals may be more related to body surface area that body weight (Oser, 1981). Assuming body surface area can be estimated by body weight$^{3/4}$, the body surface area of a 50 kG human would be about 300 times that of a 0.025 kG mouse whereas body weights differ by about 2000 times. Assuming equivalent sensitivity between mice and humans on a per unit body surface area basis (an assumption likewise by no means proven) and again, similar exposure conditions, the exposure level required to produce skin tumors would be about 1070 mG cresol/50 kg individual/day.

The maximum level of cresol reported in air in the vicinity of the Upper Ottawa Street Landfill Site was about 0.0066 ppb (or 0.0066 uG/L; Table 4.2-2, page 16, Sciex, 1982). Assuming that an individual's entire intake of cresol was from air (all consumed at the site of highest concentration on the landfill site), that the average 50 kG person breaths 20 L of air/day and that 100% of the cresol inhaled was absorbed into the body, the estimated cresol intake would be 0.13 uG/person/day. If the efficacy of cresol in causing tumors can be considered equlivalent when exposure is via the skin or the lungs and that the individuals were also exposed to appropriate promoting agents, the intake calculated above is between 8 X 10^6 and 21 X 10^6 times lower than the estimated exposure levels of cresol for the development of skin cancer extrapolated from the mouse studies.

There are other methods using various mathematical models for estimating the relative risk posed by a carcinogenic agent. These techniques require dose response data on the carcinogen and statistically adequate numbers of animals in the studies. These criteria are not meet by the studies available on cresol, therefore such methods cannot be applied. In fact, the studies published by Boutwell and Bosch (1959) were not intended for use in the estimation of human risks from exposure to the chemical agents studied; rather these investigations were designed to provide data on the mechanisms by which chemical agents produce carcinogenic responses.

CRESOL..../11

Studies of the mutagenicity of cresols, conducted in plant cell systems, have demonstrated effects (chromosomal aberrations with anaphase bridges and fragments) at sublethal concentrations on direct application of the cresol to the cells (Dean, 1978). Further studies on the mutagenicity of cresols were not available. The significance of tha above studies on plant cells with respect to the human situation is difficult to assess; nonetheless, these data further demonstrate that cresols can induce undesirable effects on direct application to cells.

Considering the magnitude of the difference in the exposure estimates derived above for the development of cancer and the levels in air around the landfill site, the threat to human health regarding cancer from cresol derived from the landfill site is considered minimal. The following factors further reduce the carcinogenic threat from cresol from the landfill site:

- the animal carcinogenicity data was collected from studies involving the direct application of 20% solutions of the individual cresol isomers to the skin. The inhalation of low levels of cresol in air undoubedly represent a much lower risk. In fact, with the exception of benzene itself, no compounds with a subsituted benzene rings containing hydroxyl or methyl groups have been shown to be systemic carcinogens although they can induce carcinogenesis through damage induced by direct contact with tissues (Dean, 1978).

- the studies to assess the potential carcinogenicity of cresols involved the pretreatment of the mice with the initiating agent DMBA. It is likely that humans may also be exposed to initiating agents also, but the likelyhood of such exposure occurring at the appropriate time in relation to the exposure to cresols would appear to be much less than in the controlled studies conducted in mice.

- the cresol levels used in the above calculations were from the site directly on the landfill with the highest air levels. It is highly unlikely that human populations would be exposed to such levels of cresols on a continuing basis.

8.2. GENERAL TOXICITY:

Like other aromatic solvents, cresol could cause irritation of dermal tissues, eyes and mucous membranes (Dean, 1978). The available data on eye irritation indicates that cresol is a relatively potent irritant (somewhat greater in potency than phenol).

CRESOL..../12

The relative similarity between LD_{50} values for oral and percutaneous routes indicates that cresol readily penetrates the skin. However, the fact that cresols can be conjugated to form glucuronide and sulfate conjugates and then rapidly excreted in urine suggests that the chemical would not accumulate in the body and, therefore, long-term systemic toxicity seems unlikely (Latham, 1970 and deBruin, 1976).

Based on the above assessment, the levels of cresol detected at the landfill site and the surrounding area are unlikely to pose a general threat to health. The available information does indicate that if health problems were related to cresol, they would be manifest by the appearence of skin rashes and skin irritation and possibly respiratory problems, particularly in sensitive individuals. These types of effects should be assessed in the general health survey of the population residing in the vicinity of the landfill.

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CRESOL..../14

APPENDIX I: DESCRIPTION OF EXPOSURE:

The following abbreviations, adopted from NIOSH (1979), were used to describe the dosage of the chemical in this toxicity profile;

TD_{lo} = Toxic Dose Low = the lowest dose of a substance introduced by any route other than inhalation over any given period of time and reported to produce any toxic effect in man or to produce carcinogenic, teratogenic, mutagenic or neoplastic effects in humans or animals.

TC_{lo} = Toxic Concentration Low = any concentration of a substance in air to which man or animals have been exposed for any given period of time and that has been reported to produce any toxic effect in man, or to produce a carcinogenic, teratogenic, mutagenic or neoplastic toxic effect in animals or humans.

LD_{lo} = Lethal Dose Low = the lowest dose of a substance, other than LD_{50}, introduced by any route other than inhalation over any given period of time and reported to have caused death in man or the lowest single dose introduced in one or more divided portions and reported to have caused death in animals.

LD_{50} = Lethal Dose Fifty = a calculated dose of a chemical substance which is expected to cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance, by any route other than inhalation, of a significant number from that population. Other lethal dose percentages, such as LD_1, LD_{10}, LD_{20}, LD_{99} etc. may also be given if available.

LC_{lo} = Lethal Concentration Low = the lowest concentration of a substance, other than an LC_{50}, in air which has been reported to have caused death in man or to have caused death in animals when they have been esposed for 24 hours or less.

LC_{50} = Lethal Concentration Fifty = a calculated concentration of a substance in air, exposure to which for 24 hours or less would cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance of a significant number from that population.

The following abbreviations were used to describe the route of administration of the substance:

Oral = administered via the mouth

Dermal = applied to the skin

ip = interperitoneally

iv = intravenously

Subcut. = injected subcutaneously

Inh = inhalation

TOXICITY PROFILE

FOR

XYLENOL

PREPARED FOR:

UPPER OTTAWA STREET
LANDFILL STUDY
SUITE 33
42 JAMES STREET SOUTH
HAMILTON, ONTARIO, CANADA
L8P 2Y4

PREPARED BY:

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January 28, 1983

TOXICITY PROFILE FOR CHEMICALS

NOTE: There are 6 isomers of xylenol; 2,3-xylenol (A - page 1)
2,4-xylenol (B - " 2)
2,5-xylenol (C - " 3)
2,6-xylenol (D - " 4)
3,4-xylenol (E - " 5)
3,5-xylenol (F - " 6)

The numbers preceeding the chemical name denote the positions of the methyl groups on the phenol ring and the information in brackets following each isomer denotes the section and page number of this toxicity profile where the available data for that isomer is presented. All xylenol isomers are consider together in Section 7 (page 7) on the overall appraisal of the potential health threat from xylenol associated with the Upper Ottawa Street Landfill Site.

All isomers have the same descriptive characteristics. Under normal environmental conditions all isomers of pure xylenol are crystalline. They are a constituent of "cresylic acid". Xylenols are only slightly soluable in water but freely soluable in alcohol, chloroform, ether, benzene and in NaOH solutions.

Xylenol (usually mixed isomers) is used in the preparation of coar-tar disinfectants and in the manufacture of artificial resins for glues, plactics etc.

1A. CHEMICAL NAME: 2,3-xylenol

2A. CAS NUMBER: 526-75-0

3A. SYNONYMS/TRADE NAMES: 2,3-dimethylphenol; phenol, 2,3-dimethyl, vic-o-xylenol; 2-hydroxy-2,3-dimethylbenzene

4A. CHEMICAL/PHYSICAL PROPERTIES:

Boiling point	218C
Melting point	75C
Molecular Weight	122.16
Molecular Formula	$C_8H_{10}O$

XYLENOL..../2

5A. GENERAL TOXICITY INDICES: (Definitions of the descriptions of exposures used in this toxicity profile are given in Appendix I, page 12 & 13)

MICE - LD_{50} (i.v.) = 56 mG/kG body weight (NIOSH, 1979).

1B. CHEMICAL NAME: 2,4-xylenol

2B. CAS NUMBER: 105-67-9

3B. SYNONYMS/TRADE NAMES: 2,4-dimethylphenol; phenol; 2,4-dimethyl, as-m-xylenol; 2,4-DMP; 2-hydroxy-2,4-dimethylbenzene

4B. CHEMICAL/PHYSICAL PROPERTIES:

Boiling point	211.5C
Melting point	25.4 - 26C
Molecular Weight	122.16
Molecular Formula	$C_8H_{10}O$

5B. GENERAL TOXICITY INDICES:

MICE - LD_{10} (ip) = 150 mG xylenol/kG body weight (NIOSH, 1979)

LD_{50} (oral) = 809 mG xylenol/kG body weight (NIOSH, 1979)

TD_{10} (skin) = 15600* mG xylenol/kG body weight (20% solution applied twice weekly) over a 39 week time period resulted in 63% skin papillomas and 42% carcinomas (Original study by Boutwell and Bosch, 1959, assessed by Schubik and Hartwell, 1972-73, NIOSH, 1979 and Sax, 1981).

TD_{10} (skin) = 5600* mG xylenol/kG body weight (10% solution applied twice weekly) over a 28 week time period resulting in 31% skin papillomas and 12% carcinomas (Original study by Boutwell and Bosch, 1959, assessed by Schubik and Hartwell, 1972-73 and Sax, 1981).

Rats - LD_{50} (oral) = 3200 mG xylenol/kG body weight (NIOSH, 1979)

LD_{50} (skin) = 1040 mG xylenol/kG body weight (NIOSH, 1979)

* Calculation of dosage in skin application studies presented in Section 7, page 7 of this toxicity profile

XYLENOL..../3

6B. CARCINOGENICITY/MUTAGENICITY:

Mice - Shown to promote carcinogenicity of the initiating agent, 9,10-dimethyl-1,2- benzanthracene (DMBA). Incidence of skin papillomas after 15 weeks treatment = 50% compared to 13% in mice treated with DMBA alone. Incidence of carcinomas in survivors was 18% at 23 weeks (Boutwell and Bosch, 1959). When tested without an initiating agent, 31% of survivors (28 weeks) developed papillomas and 12 % carcinomas (Boutwell and Bosch, 1959).

1C. CHEMICAL NAME: 2,5-xylenol

2C. CAS NUMBER: 95-87-4

3C. SYNONYMS/TRADE NAMES: 2,5-dimethylphenol; phenol, 2,5-dimethyl; p-xylenol; 2,5-DMP; 2-hydroxy-2,5-dimethylbenzene

4C. CHEMICAL/PHYSICAL PROPERTIES:

Boiling point	211.5C
Melting point	74.5C
Molecular Weight	122.16
Molecular Formula	$C_8H_{10}O$

5C. GENERAL TOXICITY INDICES:

MICE - LD_{50} (oral) = 383 mG xylenol/kG body weight (NIOSH, 1979)

TD_{10} (skin) = 5600* mG xylenol/kG body weight (10% solution applied twice weekly) over a 28 week time period resulted in 24% papillomas and 8% carcinoma (orginal study by Boutwell and Bosch, 1959; assessed by Schubik and Hartwell, 1972-73; NIOSH, 1979 and Sax, 1981)

Rats - LD_{50} (oral) = 444 mG xylenol/kG body weight (NIOSH, 1979)

Rabbits - LD_{50} (oral) = 938 mG xylenol/kG body weight (NIOSH, 1979)

* Calculation of dosage in skin application studies presented in Section, page 7 of this toxicity profile

6C. CARCINOGENICITY/MUTAGENICITY:

Mice - Not tested as a promotor of carcinogenesis. When tested in skin application studies in mice, 24% of survivors developed skin papillomas and 8% carcinomas.

1D. CHEMICAL NAME: 2,6-xylenol

2D. CAS NUMBER: 576-26-1

3D. SYNONYMS/TRADE NAMES: 2,6-dimethylphenol; phenol, 2,6-dimethyl; vic-m-xylenol; 2,6-DMP; 2-hydroxy-2,6-dimethylbenzene

4D. CHEMICAL/PHYSICAL PROPERTIES:

Boiling point	203C
Melting point	49C
Molecular Weight	122.16
Molecular Formula	$C_8H_{10}O$

5D. GENERAL TOXICITY INDICES:

MICE - LD_{50} (oral) = 479 to 980 mG xylenol/kG body weight (NIOSH, 1979)

LD_{50} (dermal) = 920 mG xylenol/kG body weight (NIOSH, 1979)

LD_{50} (ip) = 150 mG xylenol/kG body weight (NIOSH, 1979)

TD_{lo} (skin) = 4000* mG xylenol/kG body weight over 20 weeks resulted in 8% papillomas (original study by Boutwell and Bosch, 1959; assessed by Schubik and Hartwell, 1972-73 and NIOSH, 1979)

Rats - LD_{50} (oral) = 296 mG xylenol/kG body weight (NIOSH, 1979)

Rabbits - LD_{50} (oral) = 700 mG xylenol/kG body weight (NIOSH, 1979)

LD_{50} (dermal) = 1000 mG xylenol/kG body weight (NIOSH, 1979)

Primary irritation dose (eye, Draize test) = 100 mG xylenol (NIOSH, 1979)

* Calculation of dosage in skin application studies presented in Section, page 7 of this toxicity profile

XYLENOL..../5

6D. CARCINOGENICITY/MUTAGENICITY:

Mice - Shown to promote carcinogenicity of the initiating agent, 9,10-dimethyl-1,2- benzanthracene (DMBA). Incidence of skin papillomas after 15 weeks treatment = 44% compared to 13% in mice treated with DMBA alone. Incidence of carcinomas in survivors was 11% at 23 weeks (Boutwell and Bosch, 1959). When tested without an initiating agent, 8% of survivors (28 weeks) developed papillomas and 0% carcinomas (Boutwell and Bosch, 1959).

1E. CHEMICAL NAME: 3,4-xylenol

2E. CAS NUMBER: 95-65-8

3E. SYNONYMS/TRADE NAMES: 3,4-dimethylphenol; phenol, 3,4-dimethyl; as-o-xylenol; 3,4-DMP; 2-hydroxy-3,4-dimethylbenzene

4E. CHEMICAL/PHYSICAL PROPERTIES:

Boiling point	225C
Melting point	62.5C
Molecular Weight	122.16
Molecular Formula	$C_8H_{10}O$

5E. GENERAL TOXICITY INDICES:

MICE - LD_{50} (oral) = 400 mG xylenol/kG body weight (NIOSH, 1979)

TD_{10} (skin) = 4000* mG xylenol/kG body weight over 28 weeks resulted in 50% skin papillomas and 14% carcinomas (Original study by Boutwell and Bosch, 1959, assessed by Schubik and Hartwell, 1972-73; NIOSH, 1979 and Sax, 1981)

Rats - LD_{50} (oral) = 500 mG xylenol/kG body weight (NIOSH, 1979)

Rabbits - LD_{50} (oral) = 800 mG xylenol/kG body weight (NIOSH, 1979)

* Calculation of dosage in skin application studies presented in Section, page 7 of this toxicity profile

6E. CARCINOGENICITY/MUTAGENICITY:

Mice - Shown to promote carcinogenicity of 9,10-dimethyl-1,2-benzanthracene (DMBA). Incidence of skin papillomas after 15 weeks treatment = 95% compared to 13% in mice treated with DMBA alone. Incidence of carcinomas in survivors was 14% at 23 weeks.(Boutwell and Bosch, 1959).

1F. CHEMICAL NAME: 3,5-xylenol

2F. CAS NUMBER: 108-68-9

3F. SYNONYMS/TRADE NAMES: 3,5-dimethylphenol; phenol, 3,5-dimethyl; sym-m-xylenol; 3,5-DMP; 2-hydroxy-3,5-dimethylbenzene

4F. CHEMICAL/PHYSICAL PROPERTIES:

Boiling point	219.5C
Melting point	64C
Molecular Weight	122.16
Molecular Formula	$C_8H_{10}O$

5F. GENERAL TOXICITY INDICES:

MICE - LD_{50} (oral) = 477 mG xylenol/kG body weight (NIOSH, 1979)

TD_{lo} (skin) = 4000* mG xylenol/kG body weight over 28 weeks resulted in 55% with papillomas and 14% with carcinomas (Original study by Boutwell and Bosch, 1959, assessed by Schubik and Hartwell, 1972-73; NIOSH, 1979 and Sax, 1981)

Rats - LD_{50} (oral) = 608 mG xylenol/kG body weight (NIOSH, 1979)

Rabbits - LD_{50} (oral) = 1313 mG xylenol/1G body weight (NIOSH, 1979)

Primary irritation dose (eye, Draize test) = 726 mG xylenol (produced severe effect, NIOSH, 1979)

* Calculation of dosage in skin application studies presented in Section, page 7 of this toxicity profile

6F. CARCINOGENICITY/MUTAGENICITY:

Mice - Shown to promote carcinogenicity of 9,10-dimethyl-1,2-benzanthracene (DMBA). Incidence of skin papillomas after 15 weeks treatment = 40% compared to 13% in mice treated with DMBA alone. Incidence of carcinomas in survivors was 5% at 23 weeks.(Boutwell and Bosch, 1959).

7. APPRAISAL OF POTENTIAL HAZARD FROM XYLENOL ASSOCIATED WITH THE UPPER OTTAWA STREET LANDFILL SITE:

The animal toxicity data on the various isomers of xylenol focused primarily on carcinogenesis, acute toxicity and eye irritation. Toxicity data from exposed human subjects was not available. In this appraisal of the potential health threat related to xylenol from the landfill site, carcinogenesis will be discussed first.

7.1. CARCINOGENESIS:

The available carcinogenicity data was collected from skin application studies in mice, usually designed to assess tumor promoting activity. For the purpose of gaining some crude indication of risks to humans from such studies, the dosage of xylenol was transposed from so many drops of a known percent solution of xylenol per application to mG xylenol/kG body weight/treatment period. The standard equation for this transposition was as follows:

$$\text{Total dose (D)} = \frac{d \times c \times f \times t}{W}$$

Where: d = volume of one drop (assumed to be 0.025 mL)
c = concentration of solution used (mG xylenol/mL)
f = frequency of applications per week
t = number of weeks treatment
W = body weight of a mouse (assumed to be 0.025 kG)

(Similar calculations were made by Schubik and Hartwell, 1972-73 and NIOSH, 1979 in the assessment of the carcinogenicity data on xylenol.)

XYLENOL..../8

It must be stressed that the process of extrapolating carcinogenicity data from observations made on laboratory animals to the humans situation is far from exact. Questions of species differences in response to the agent, the possible differences in response induced by studying high dosages of the agent, lack of knowledge on the mechanism of action of most toxicants (particularly carcinogens) and the difficulties of extrapolating data outside the range of experimental observations to estimate levels of risks encountered in human populations, all contribute to the uncertainity of the process. Nevertheless, crude indications of the magnitude of hazard associated with exposure to a chemical agent can be gained from such assessments.

Most of the skin application carcinogenicity studies in mice involved treatment with xylenol over 28 weeks. The lowest dose of xylenol that produced a carcinogenic response in these studies was 4000 mG/kG body weight over 28 weeks. Assuming equivalent sensitivity between mice and humans on a per kilogram body weight basis (an assumption by no means proven), the exposure level in humans required to produce skin tumors would be about 4000 mG xylenol/kG body weight/28 weeks or about 1020 mG xylenol/50 kG individual/day.

The response relationship between different species of animals may be more related to body surface area that body weight (Oser, 1981). Based on the estimation of body surface area as body weight$^{3/4}$, the body surface area of a 50 kG human would be about 300 times that of a 0.025 kG mouse whereas body weights differ by about 2000 times. Assuming equivalent sensitivity between mice and humans on a per unit body surface area basis (an assumption likewise by no means proven), the exposure level required to produce skin tumors would be about 380 mG xylenol/50 kg individual/day.

The maximum level of xylenol reported in air in the vicinity of the Upper Ottawa Street Landfill Site was about 1.25 ppb (Table 4.2-2, page 16, Sciex, 1982). Assuming that an individual's entire intake of xylenol was from air (all consumed at the site of highest concentration on the landfill site) and that the average 50 kG person breaths 20 L of air/day, the estimated xylenol intake would be 25 uG/person/day. If the efficacy of xylenol in causing tumors can be considered equlivalent when exposure is via the skin or the lungs, this intake is between 15000 and 40000 time below the estimated exposure levels of xylenol for the development of skin cancer extrapolated from the mouse studies.

There are other methods using various mathematical models for estimating the relative risk posed by a carcinogenic agent. These techniques require dose response data on the carcinogen and statistically adequate numbers of animals in the studies. These criteria are not meet by the studies available on xylenol, therefore such methods cannot be applied.

XYLENOL..../9

Considering the magnitude of the difference in the exposure estimates derived above for the development of cancer and the levels of xylenol in air around the landfill site, the threat to human health regarding cancer from xylenol derived from the landfill site is considered minimal. The following factors further reduce the carcinogenic threat from xylenol from the landfill site:

- the animal carcinogenicity data was collected from studies involving the direct application of fairly concentrated solutions of xylenol (10 to 20%) to the skin. The inhalation of low levels of xylenol (a few ppb) in air undoubedly represent a much lower risk. In fact, with the exception of benzene itself, no compounds with benzene rings subsituted with hydroxyl or methyl groups have been shown to be systemic carcinogens although they can induce carcinogenesis through damage induced by direct contact with tissues (Dean, 1978).

- the analytical data reported for xylenol levels associated with the landfill site (Sciex, 1982) represents a mixture of isomers. The available carcinogenicity data demonstrate that not all isomers are of equal potency in inducing skin tumors. The data for the most potent of the isomers was used in estimating the exposure levels above;

- the xylenol levels used in the above calculations were from the site directly on the landfill with the highest air levels;

- the levels of xylenol were considerable higher (44.54 ppb versus 1.25 ppb) in locations remote to from the landfill per se (Sciex, 1982).

7.2. GENERAL TOXICITY:

There is less data available on the toxicity of xylenol (as distinct from carcinogenesis). Some insite into the potential toxicology of xylenol can be gained from data on related chemicals such as the xylenes. Xylenol isomers can be formed in biological systems from the aromatic hydoxylation of xylenes. It has been clearly demonstrated, and indeed would be predicted based on chemical stuructures, that xylenols are rapidly exceted in urine either unchanged or as conjugates of glucuronides and sulphates (Latham, 1970 and De Bruin, 1976). Xylenes are also known to be metabolized through methyl benzyl alcohols to toluic acid whereas xylenols are not. Therefore, some of the toxic effects of xylenol would be expected to be similar to the xylenes but of a lesser magnitude (Dean, 1978).

XYLENOL..../10

Commercial xylene mixtures have been shown to be teratogenic in the mouse (Marks, et al, 1982) but only at doses that produced overt toxicity in the dams. Since xylenols are more rapidly excreted that xylenes, the threat of adverse reproductive effects associated with xylenol from the landfill site is highly unlkiely.

Like other aromatic solvents, xylenol could cause irritation of dermal tissues, eyes and mucous membranes (Dean, 1978). The available data on eye irritation indicates that xylenol is a relatively potent irritant and that differences exist between isomers in this respect (NIOSH, 1979). Xylenes are reportedly more acutely toxic than toluene or benzene (Gerarde, 1962) and more necrotizing than benzene (Wilson et al, 1948). The similarities between xylenol and xylene suggest that the most likely health threat would be related to irritant-like effects on the skin and mucous membranes.

The relative similarity between LD_{50} values for oral and percutaneous routes indicates that xylenol readily penetrates the skin. However, the fact that xylenol is rapidly excreted in urine suggests that the chemical would not accumulate in the body and, therefore, long-term systemic toxicity seems unlikely.

Based on the above assessment, the levels of xylenol detected at the landfill site and the surrounding area are unlikely to pose a general threat to health. The available information does indicate that if health problems were related to xylenol, they would be manifest by the appearence of skin rashes and skin irritation and possibly minor respiratory problems, particularly in sensitive individuals. These types of effects should be assessed in the general health survey of the population residing in the vicinity of the landfill.

APPENDIX I: DESCRIPTION OF EXPOSURE:

The following abbreviations, adopted from NIOSH (1979), were used to describe the dosage of the chemical in this toxicity profile;

TD_{lo} = Toxic Dose Low = the lowest dose of a substance introduced by any route other than inhalation over any given period of time and reported to produce any toxic effect in man or to produce carcinogenic, teratogenic, mutagenic or neoplastic effects in humans or animals.

TC_{lo} = Toxic Concentration Low = any concentration of a substance in air to which man or animals have been exposed for any given period of time and that has been reported to produce any toxic effect in man, or to produce a carcinogenic, teratogenic, mutagenic or neoplastic toxic effect in animals or humans.

LD_{lo} = Lethal Dose Low = the lowest dose of a substance, other than LD_{50}, introduced by any route other than inhalation over any given period of time and reported to have caused death in man or the lowest single dose introduced in one or more divided portions and reported to have caused death in animals.

LD_{50} = Lethal Dose Fifty = a calculated dose of a chemical substance which is expected to cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance, by any route other than inhalation, of a significant number from that population. Other lethal dose percentages, such as LD_1, LD_{10}, LD_{20}, LD_{99} etc. may also be given if available.

LC_{lo} = Lethal Concentration Low = the lowest concentration of a substance, other than an LC_{50}, in air which has been reported to have caused death in man or to have caused death in animals when they have been esposed for 24 hours or less.

LC_{50} = Lethal Concentration Fifty = a calculated concentration of a substance in air, exposure to which for 24 hours or less would cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance of a significant number from that population.

8. REFERENCE MATERIAL:

Boutwell, R.K. and D.K. Bosch. 1959. The tumor promoting action of phenol and related compounds for mouse skin. Cancer Res. 19:413-424

Dean, B.J. 1978. Genetic toxicology of benzene, toluene, xylenes and phenols. Mutation Res. 47:75-97.

De Bruin, A. 1976. Biochemical toxicology of environmental agents. Elsevier/North Holland Biomedical Press, Amsterdam.

Gerarde, H.W. 1962. Xylene, $C_6H_4(CH_3)_2$ (xylol, dimethylbenzene). In: Industrial Hygiene and Toxicology, ed. F.A. Patty, 2nd rev. ed., vol. 2, New York:Interscience.

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Marks, T.A., T.A. Ledoux and J.A. Moore. 1982. Teratogenicity of a commercial xylene mixture in the mouse. J. Toxicol. Environ. Health 9:97-105.

National Institute for Occupational Safety and Health. 1979. Occupational health guidelines for phenol. NIOSH/OSHA Occupational Health Guidelines for Chemical Hazards. Mackison, F.W. and R.S. Stricoff, Eds. DHHS(NIOSH) Publication Number 81-123.

Oser, B.L. 1981. The rat as a model for human toxicological evaluation. J. Toxicol. Environ. Health 8:521-542.

Sax, N.I. 1981. Cancer causing chemicals. Van Norstrand Reinhold Co., N.Y. & Toronto.

Schubik, P. and J.L. Hartwell. Survey of compounds which have been tested for carcinogenic activity. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health. Publication Number 149, 1961-67, 1968-69, 1970-71 and 1972-73. (After 1970 known as the NCI Monographs)

Sciex, 1982. Draft Report. Air quality surveys of Upper Ottawa Street Landfill Study. Prepared for Upper Ottawa Street Landfill Study, Suite 33, 42 James Street South, Hamilton, Ontario, L8P 2Y4.

Wilson, R.H., G.V. Hough and W.E. McCormick. 1948. Medical problems encountered in the manufacture of American-made rubber. Ind. Med. 17:199-207.

The following abbreviations were used to describe the route of administration of the substance:

Oral = administered via the mouth

Dermal = applied to the skin

ip = interperitoneally

iv = intravenously

Subcut. = injected subcutaneously

Inh = inhalation

TOXICITY PROFILE

FOR

PHENOL

PREPARED FOR:

UPPER OTTAWA STREET
LANDFILL STUDY
SUITE 33
42 JAMES STREET SOUTH
HAMILTON, ONTARIO, CANADA
L8P 2Y4

PREPARED BY:

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Consultant Toxicologist
F.D.C. Consultants, Inc.
Orono, Ontario, Canada
LOB 1MO.
January 28, 1983

TOXICITY PROFILE FOR CHEMICALS

1. CHEMICAL NAME: Phenol

2. CAS NUMBER: 108-95-2

3. SYNONYMS/TRADE NAMES: carbolic acid; monohydroxybenzene

4. CHEMICAL/PHYSICAL PROPERTIES:

Description	colorless to pink solid or thick liquid with a sweet, tar-like odor.
Boiling Point	182.0C
Melting Point	41.0C
Molecular Formula	C_6H_5OH
Molecular Weight	94.11
Specific Gravity	1.07(solid); 1.05(liquid)
Vapour Density	3.24
Vapour Pressure	0.36 mm Hg
Water Solubility	8.4 G/100G at 20C

5. SOURCES/USES:

curing resins; adhesives; industrial coatings; synthesis of resins; agricultural chemicals; pharmaceuticals; perfumes; refining lubricating oils; waxes; gasoline additive.

6. REGULATORY INFORMATION/EXPOSURE LIMITS/ETC.:

PEL = 5 ppm/8 hours (19 to 20 mG/M^3); maximum 15 minute peak of 60 mG/M^3.

Odor threshold = 0.3 to 3 ppm.

7. GENERAL TOXICITY INDICES: (Definitions of the descriptions of exposures used in this toxicity profile are given in Appendix I, page 10)

Mice - TD_{10} (skin) = 4800* mG phenol/kG body weight (20% solution applied twice weekly) over a 12 week time period resulted in 63% skin papillomas and 0% carcinomas (Original study by Boutwell and Bosch, 1959, assessed by Schubik and Hartwell, 1972-73, NIOSH, 1979 and Sax, 1981).

* Calculation of dosage in skin application studies is presented in Section 12, page 5 of this toxicity profile

PHENOL..../2

TD_{10} (skin) = 2400* mG phenol/kG body weight (5% solution applied twice weekly following pre-treatment of the mice with dimethylbenzanthrene) over a 24 week time period resulted in 56% skin papillomas and 20% carcinomas (Original study by Boutwell and Bosch, 1959, assessed by Schubik and Hartwell, 1972-73, NIOSH, 1979 and Sax, 1981).

Rats - LD_{50} (percutaneous) = 0.625 mL phenol/kG body weight (Conning and Hayes, 1970).

LD_{50} (oral) = 0.65G/kG body weight (Flickinger 1976).

Rabbits - LD_{50} (percutaneous) = 0.85G/kG body weight (range 0.60 to 1.20 G/kG) (Flickinger 1976).

Humans - Lethal dose (oral) = 1G (NIOSH, 1978) to between 2 and 15 G (Niyogi, 1973). Blood phenol levels of 9 mG% were reported in one fatal case (Niyogi, 1973) NIOSH (1978) reports that urinary phenol levels (free plus conjugated) of workers manufacturing phenol-formalhehyde plastics were proportional to air concentrations up to 12.5 mG phenol/M^3 of workroom air.

8. GENERAL SYMPTOMS/SIGNS OF EXPOSURE:

Rats - Inhalation at 30 to 60 ppm results in respiratory inhibition, liver damage and paralysis (NIOSH, 1978).

Studies in rats showed severe skin lesions from the direct application of phenol, including edema, erythema, discoloration and necrosis. Within 5 to 10 minutes of application of the phenol to the skin, muscle tremors and twitching were observed. These signs progressed to convulsions, prostration and death. Between 45 and 90 minutes after application of phenol to the skin hemoglobinuria was evident with to renal congestion and hematin casts in the urine (Conning and Hayes, 1970).

PHENOL..../3

Dilution of phenol with water reduced the corrosive reaction to the skin but actually increased the systemic toxicity of phenol about five fold. Conning and Hayes (1970) attributed the increased toxicity of diluted phenol to greater absorption through the skin due to reduced dermal damage.

Rabbits - Flickinger (1976) demonstrated skin lesions in rabbits following dermal applications of phenol. A dermal dose of 0.5G resulted in severe necrosis. The application of 0.1G to the eyes of rabbits resulted in inflammation and conjunctivitis that developed into keratoconus and pannu formation over 14 days of observation. Flickinger (1976) classified phenol as a corrosive substance rather than a primary irritant.

Humans - Phenol poisoning following long-term exposure is typified by vomiting, anorexia, dark urine, diarrhea, dizziness, headache, skin discoloration and liver damage.

Phenol in the vapour form or in solution is an irritant to the eyes, mucous membranes (nose, throat and mouth) and the skin. Contact with the skin results in local anesthesia with white discoloration of the area and the subsequent development of a gangrenous condition. Occupational exposures over a prolonged period of time can result in severe dermatitis leading to ochronosis in some cases. Systemic effects are observed in liver, kidney and central nervous system (NIOSH, 1978).

NIOSH (1978) does not report any human fatalities from the inhalation of phenol vapours. Poisoning of a laboratory technician repeatedly exposed to phenol vapours and liquid spilled on the skin is reported by NIOSH (1978). Symptoms included anorexia, weight loss, weakness, muscle aches and pains and dark urine. These symptoms gradually disappeared during several months of non-exposure to phenol. Re-exposure produced an immediate worsening of symptoms including prompt darkening of the urine and tender enlargement of the liver.

The oral ingestion of lethal amounts of phenol causes severe burns of the mouth and throat, marked abdominal pain, cyanosis, muscular weakness, collapse, coma and dealth. Tremors, convulsions and muscular twitching can be observed but these symptoms are usually not severe.

PHENOL..../4

9. MUTAGENICITY:

Bacteria - Phenol has been shown to be mutagenic in E. Coli (Demeric, et al, 1951) and Drosophila (Hadorn and Niggli, 1946).

Cell cultures -
Moromoto and Wolff (1980) demostrated that phenol increased the rate of sister chromatid exchange in human lymphocyte cell cultures. Phenol was classed as a weak mutagen.

10. CARCINOGENICITY:

Mice - About 12 studies have demonstrated that phenol is a weak carcinogen and can act as a promoter of carcinogenesis in combination with initiating agents such as croton oil, croton resin (a phorbol ester) and dimethylbenzanthracene (DMBA). Positive carcinogenic responses in laboratory mice required dermal exposure to high levels of phenol. The procedures followed in these studies generally involved clipping the fur from an area of the back of the mice then applying the phenol directly to the skin. If the study involved the use of initiating agents, such materials were applied in a single dose, prior to the application of the promoting agent, to the same area of skin. If the study was designed to assess co-carcinogenesis, the two to be tested for co-carcinogenic activity were applied to the same area of skin simultaneously

The tumor promoting response was strain dependent. Using Sutter mice (Black) treated with phenol, Boutwell and Bosch (1959) reported skin papillomas in between 33% and 95% of the treated mice over 5 different studies. The phenol concentrations used ranged from 5% to 20% and was applied with benzene or dioxane as a solvent. The incidence of papillomas following similar treatment protocols using CAF_1 or C_3H mice was zero. Holtzman and Albino-Sutter strains of mice were intermediate in the development of papillomas following phenol treatment.

Shamberger (1971) demonstrated that treatment of the skin with B-carotene, vitamin A or retinol reduced the development of skin papillomas following phenol treatment and with DMBA as an initiating agent in combination with phenol as a promoting agent. Shamberger (1971) suggested that those compounds that depressed the activity of acid phosphatase and aryl sulfatase enzymes tended to increase the development of skin papillomas in mice.

Humans - The most significant finding in the assessment of the carcinogenicity data on phenol was that there is no evidence associating phenol exposure with the development of cancer in humans.

11. REPRODUCTIVE EFFECTS/TERATOGENICITY:

There is no evidence that phenol exposure results in untoward reproductive effects probably due to the high acute toxicity of phenol and its rapid rate of excretion. At low doses the compound would be conjugated and excreted; at high doses the acute toxic effects of phenol results in lethality.

12. APPRAISAL OF THE POTENTIAL HAZARD FROM PHENOL ASSOCIATED WITH THE UPPER OTTAWA STREET LANDFILL SITE:

The animal toxicity data on the various isomers of phenol focused primarily on carcinogenesis, acute toxicity and eye irritation. Toxicity data from human subjects exposed in occupational settings indicated that the phenol isomers are severe contact irritants. In this appraisal of the potential health threat related to phenol from the landfill site, carcinogenesis will be discussed first.

12.1. CARCINOGENESIS:

The available carcinogenicity data was collected from skin application studies in mice, usually designed to assess tumor promoting activity by pretreating the animals with DMBA. For the purpose of gaining some crude indication of risks to humans from such studies, the dosage of phenol was transposed from so many drops of a known percent solution of phenol per application to mG phenol/kG body weight/treatment period. The standard equation for this transposition was as follows:

$$\text{Total dose (D)} = \frac{d \times c \times f \times t}{W}$$

Where: d = volume of one drop (assumed to be 0.025 mL)
c = concentration of solution used (mG phenol/mL)
f = frequency of applications per week
t = number of weeks treatment
W = body weight of a mouse (assumed to be 0.025 kG)

(Similar calculations were made by Schubik and Hartwell, 1972-73 and NIOSH, 1979 in the assessment of the carcinogenicity data on phenol.)

It must be stressed that the process of extrapolating toxicity on carcinogenicity data from observations made on laboratory animals to the humans situation is far from exact. Questions of species differences in response to the agent, the possible differences in response induced by studying high dosages of the agent, lack of knowledge on the mechanism of action of most toxicants (particularly carcinogens) and the difficulties of extrapolating data outside the range of experimental observations to estimate levels of risks encountered in human populations, all contribute to the uncertainity of the process. Nevertheless, crude indications of the magnitude of hazard associated with exposure to a chemical agent can be gained from such assessments.

The carcinogenicity studies with the phenol in mice involved skin application twice weekly for 12 weeks. Assuming equivalent sensitivity between mice and humans on a per kilogram body weight basis (an assumption by no means proven) and similar exposure conditions, the exposure level in humans required to produce skin tumors would be about 4800 mG phenol/kG body weight/12 weeks or about 2800 mG phenol/50 kG individual/day (assuming the average person weighs 50 kG).

The response relationship between different species of animals may be more related to body surface area that body weight (Oser, 1981). Assuming body surface area can be estimated by body weight$^{3/4}$, the body surface area of a 50 kG human would be about 300 times that of a 0.025 kG mouse whereas body weights differ by about 2000 times. Assuming equivalent sensitivity between mice and humans on a per unit body surface area basis (an assumption likewise by no means proven) and again, similar exposure conditions, the exposure level required to produce skin tumors would be about 1070 mG phenol/50 kg individual/day.

The maximum level of phenol reported in air in the vicinity of the Upper Ottawa Street Landfill Site was about 0.23 ppb (or 0.23 uG/L; Table 4.2-2, page 16, Sciex, 1982). Assuming that an individual's entire intake of phenol was from air (all consumed at the site of highest concentration on the landfill site), that the average 50 kG person breaths 20 L of air/day and that 100% of the phenol inhaled was absorbed into the body, the estimated phenol intake would be 4.6 uG/person/day. If the efficacy of phenol in causing tumors can be considered equlivalent whether exposure is via the skin or the lungs and that the individuals were also exposed to appropriate promoting agents, the intake calculated above is between 6×10^5 and 2×10^5 times lower than the estimated exposure levels of phenol for the development of skin cancer extrapolated from the mouse studies.

There are other methods using various mathematical models for estimating the relative risk posed by a carcinogenic agent. These techniques require dose response data on the carcinogen and statistically adequate numbers of animals in the studies. These criteria are not meet by the studies available on phenol, therefore such methods cannot be applied. In fact, the studies published by Boutwell and Bosch (1959) were not intended for use in the estimation of human risks from exposure to the chemical agents studied; rather these investigations were designed to provide data on the mechanisms by which chemical agents produce carcinogenic responses.

The carcinogenic risk to humans from phenol from the landfill site should be considered minimal. The evidence from animal studies (primarily mice) indicates that phenol is a weak promoter, a very weak carcinogen and actually inhibits tumor formation in cocarcinogenesis experiments (Van Duuren, 1982). These responses were observed in studies in mice employing very high concentrations of phenol applied directly to the skin. The relevance of such data to the evaluation of human risks in occupational settings is questionable and it is extremely doubtful if it has any relationship to the situation at the Upper Ottawa Landfill Site where the maximum phenol concentrations detected were 0.23 ppb (Sciex 1982).

12.2. GENERAL TOXICITY:

Phenol has been shown to be an irritant to the skin, eyes and upper respiratory tract, particularly in occupational settings. Such effects are noted at the low ppm concentration range, at or near the odor threshold for phenol. The possibility of sensitive population groups developing such effects or of phenol interacting with other agents associated with the home or the landfill site to produce such effects cannot be completely ruled out. In the course of assessing the health status of populations residing near the landfill site, consideration should be given to respiratory problems, various sensitization of the immune system, skin disorders, etc.

13. REFERENCE MATERIAL:

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Boutwell, R.K. and D.K. Bosch. 1959. The tumor promoting action of phenol and related compounds for mouse skin. Cancer Res. 19:413-424

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Shamberger, R.J. 1971. Inhibitory effect of vitamin A on carcinogenesis. J. National Cancer Institute 47:667-673.

Sciex, 1982. Draft Report. Air quality surveys of Upper Ottawa Street Landfill Study. Prepared for Upper Ottawa Street Landfill Study, Suite 33, 42 James Street South, Hamilton, Ontario, L8P 2Y4.

Van Duuren, B.L., A. Sivak, L. Langseth, B.M. Goldschmidt and A. Segal. 1968. Initiators and promoter in tabacco carcinogenesis. National Cancer Institute Monograph 28:173-180.

Van Duuren, B.L., T. Blazej, B.M. Goldschmidt, C. Katz, S. Melchionne and A. Sivak. 1971. Co-carcinogenesis studies on mouse skin and inhibition of tumor induction. J. National Cancer Institute 46:1039-1044.

Van Duuren, B.L. 1982. Cocarcinogens and tumor promoters. J. Am. Coll. Toxicol. 1:17-27.

APPENDIX I: DESCRIPTION OF EXPOSURE:

The following abbreviations, adopted from NIOSH (1979), were used to describe the dosage of the chemical in this toxicity profile;

TD_{lo} = Toxic Dose Low = the lowest dose of a substance introduced by any route other than inhalation over any given period of time and reported to produce any toxic effect in man or to produce carcinogenic, teratogenic, mutagenic or neoplastic effects in humans or animals.

TC_{lo} = Toxic Concentration Low = any concentration of a substance in air to which man or animals have been exposed for any given period of time and that has been reported to produce any toxic effect in man, or to produce a carcinogenic, teratogenic, mutagenic or neoplastic toxic effect in animals or humans.

LD_{lo} = Lethal Dose Low = the lowest dose of a substance, other than LD_{50}, introduced by any route other than inhalation over any given period of time and reported to have caused death in man or the lowest single dose introduced in one or more divided portions and reported to have caused death in animals.

LD_{50} = Lethal Dose Fifty = a calculated dose of a chemical substance which is expected to cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance, by any route other than inhalation, of a significant number from that population. Other lethal dose percentages, such as LD_1, LD_{10}, LD_{20}, LD_{99} etc. may also be given if available.

LC_{lo} = Lethal Concentration Low = the lowest concentration of a substance, other than an LC_{50}, in air which has been reported to have caused death in man or to have caused death in animals when they have been esposed for 24 hours or less.

LC_{50} = Lethal Concentration Fifty = a calculated concentration of a substance in air, exposure to which for 24 hours or less would cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance of a significant number from that population.

The following abbreviations were used to describe the route of administration of the substance:

Oral = administered via the mouth

Dermal = applied to the skin

ip = interperitoneally

iv = intravenously

Subcut. = injected subcutaneously

Inh = inhalation

TOXICITY PROFILE

FOR

CARBARYL

PREPARED FOR:

UPPER OTTAWA STREET
LANDFILL STUDY
SUITE 33
42 JAMES STREET SOUTH
HAMILTON, ONTARIO, CANADA
L8P 2Y4

PREPARED BY:

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Orono, Ontario, Canada
LOB 1MO.
April 8, 1983

TOXICITY PROFILE FOR CHEMICALS

1. CHEMICAL NAME:
   Carbamic acid, methyl-, naphthalenyl ester (NIOSH, 1982)

2. CAS NUMBER:
   63-25-2

3. SYNONYMS/TRADE NAMES: (Hayes, 1982; NIOSH, 1982)
   Carbaril (Italian); Arylam; Atoxan; Caprolin; Carbamine; Carbaryl; Carbaryl (DOT); Carbatox; Carbatox-60; Carbatox-75; Carpolin; Compound 7744; Crag Seven; Denapon; Dicarbam; Ent 23,969; Experimental Insecticide 7744; Bamonil; Germain's; Hexavin; Karbaryl (Polish); Karaspray; Karbatox; Karbosep; N-methylcarbamate de 1-naphthyle (French); Methylcarbamate 1-naphthalenol; methylcarbamate 1-naphthol; methylcarbamic acid; 1-naphthyl ester; N-methyl-1-naftyl-carbamaat (Dutch); N-methyl-1-naphthyl-carbamat (German); N-methyl-alpha-naphthylcarbamate; N-methyl-1-naphthylcarbamate; N-methyl-alpha--naphthylurethan; N-methyl-1-naftil-carbamamato (Italian); NAC; alpha-naftyl-N-methylcarbamat (Czech); 1-Naphthyl-N-methylcarbamate; 1-naphthyl methylcarbamate; alpha-naphthyl N-methylcarbamate; 1-naphthyl N-methylcarbamate; Tricarnam; UC 7744; Union Carbide 7,744

4. CHEMICAL/PHYSICAL PROPERTIES: (Hayes, 1982; NIOSH, 1982)

Density	1.232 @ 20C
Description	Carbaryl is a white, crystaline solid stable to light, heat and hydrolysis under normal storage conditions. Carbaryl rapidly hydrolyzes at pH 10, therefore is not compatible with lime formulations.
Melting Point	145C
Molecular Formula	$C_{12}H_{11}NO_2$
Molecular Weight	201.24
Solubility	40 ppm in water @ 30C; moderately soluable in polar solvents and about 5% soluable in petroleum oils
Vapour Pressure	less than 0.005 mm Hg @ 26C

5. SOURCES/USES:

   Is a contact insecticide with slight systemic properties. Is available as a wettable powder, emmulsifiable concentrate and in the form of dusts

CARBARYL..../2

6. REGULATORY INFORMATION/EXPOSURE LIMITS/ETC.:

TLV (with time weighted average) = 5 mG/M^3 (NIOSH, 1982);

7. GENERAL TOXICITY INDICES: (Definitions of the descriptions of exposures used in this toxicity profile are given in Appendix I, page 15 & 16)

MICE

LD_{50} (oral) = 438 mG/kG (NIOSH, 1982; Kuhr and Dorough, 1976; Rybakova, 1966)

LD_{50} (oral) = 650 mG/kG (Hayes, 1982; Coulston, 1966)

LD_{50} (oral) = 116 mG/kG (females) & 108 mG/kG (males) (Hayes, 1982; Haley et al, 1974)

LD_{50} (ip) = 25 mG/kG (NIOSH, 1982, Baron, et al, 1964)

LD_{50} (ip) = 29 mG/kG (Hayes, 1982; Balba and Casida, 1968)

Rats

LD_{50} (oral) = 250 mG/kG (NIOSH, 1982; Vanderkar et al, 1971)

LD_{50} (oral) = 850 mG/kG (males) & 500 mG/kG females (Hayes, 1982; Gaines, 1960)

LD_{50} (oral) = 510 mG/kG (Hayes, 1982; Carpenter et al, 1961)

LD_{50} (oral) = 515 mG/kG (Hayes, 1982; Rybakova, 1966)

LD_{50} (oral) = 600 mG/kG (Hayes, 1982; Coulston, 1966)

LD_{50} (inhalation) = 721 mG/kG (NIOSH, 1982)

LD_{50} (skin) = 4000 mG/kG (NIOSH, 1982)

LD_{50} (skin) = greater than 4000 mG/kG (Hayes, 1982; Gaines, 1960)

LD_{50} (ip) = 48 mG/kG (NIOSH, 1982; Brodeur and Dubois, 1963)

LD_{50} (ip) = 200 mG/kG (Hayes, 1982; Wilhelm and Vandekar, 1966)

	LD_{50} (iv) = 42 mG/kG (NIOSH, 1982; Hayes, 1982; Vanderkar et al 1971; Wilhelm and Vandekar, 1966)
	LD_{50} (iv) = 24 mG/kG (Hayes, 1982; Carpenter et al, 1961)
	LD_{50} (not known) = 500 mG/kG (NIOSH, 1982; Kuhr and Dorough, 1976)
Hamster	LD_{10} (oral) = 250 mG/kG (NIOSH, 1982; Robens, 1969)
Guinea Pig	LD50 (oral) = 280 mG/kG (NIOSH, 1982)
Rabbit	LD_{50} (oral) = 710 mG/kG (NIOSH, 1982)
	LD_{50} (skin) = 2000 mG/kG (NIOSH, 1982)
	LD_{50} (ip) = 223 mG/kG (Hayes, 1982; Carpenter et el, 1961)
Cat	LD_{50} (oral) = 150 mG/kG (NIOSH, 1982)
Dog	LD_{50} (oral) = greater than 500 mG/kG (Hayes, 1982; Coulston, 1066)
Monkey	LD_{50} (oral) = greater then 1000 mG/kG (Hayes, 1982; Coulston, 1966)
Chicken	LD_{50} (oral) = 197 mG/kG (NIOSH, 1982; Schermann and Ross, 1961)
Wild Bird	LD_{50} (oral) = 56 mG/kG (NIOSH, 1982; Schafer, 1972)

CARBARYL..../4

8. GENERAL SYMPTOMS/SIGNS OF EXPOSURE:

The acute toxic effects of carbaryl are typical of cholinesterase inhibition, including various alterations in central and peripheral nervous system functions with secondary changes in the cardiorespiratory system, kidney, etc. Carbaryl is inherantly toxic as evident from the acute toxicity data. Administration via the intravenous or interperitoneal routes results in acute toxic effects at 1/10th to 1/20th the dose required when administered orally, dermally or by inhalation (see Section 7). It has been proposed that the lower acute toxicity when administered via these routes may related to limited absorption although the high rate of metabolism of carbaryl and the rapid recovery of the inhibited cholinesterase may also be involved (Hayes, 1982). However, Ahdaya and Guthrie (1982) have demonstrated that the absorption of carbaryl from the gastrointestinal tract may be as high as 68% of the total oral dose over a 1 hour period. These data suggest that metabolism and distribition patterns may be more important in explaining the differences in potency of carbaryl by different routes of administration.

The toxicological consequences of repeated exposure to carbaryl are less well understood. The toxicity reported appears to vary between investigators and Hayes (1982) indicated that this suggests differences in the composition of comercial products available in different countries. The differences are particularly evident regarding reproductive effects . Also, certain species, i.e. swine, display effects following low level, multi-dose exposure that are not related to cholinesterase inhibition (Hayes, 1982).

High level exposure of rats (2250 ppm in the diet or about 110 mG/kG/day) for over 90 days resulted in increased kidney weights, increased relative liver weights and decreased body weight gains. A dietary level of 200 ppm (8 mG/kG/day) over 2 years produced no measurable effects on mortality, longevity, organ weights and the incidence of neoplasia and or tissue histopathology (Carpenter et al, 1961).

No effects on growth, organ weights, hematology, cholinesterase levels, a variety of biochemical parameters or tissue histopathology were observed in dogs receiving up to 7.2 mG/kG/day for 1 year (Carpenter et al, 1961).

Swine fed 150 mG carbaryl/kG/day developed myasthenia, incoordination, ataxia, intension tremors and clonic muscular contractions resulting in marked debility after 45 days treatment and prostration after 72 days or more (Hayes, 1982). Significant histopathological observations were restricted to the central nervous system and skeletal musculature. CNS lesions included vascular changes (endothelial hypertrophy, hyalinzation of vascular walls and hemorrhage) with secondary myelinization of nerve tracts in the brain stem and cerebellar peduncles. Muscle lesions included hyaline and vacuolar degeneration. From the appearance of dark urine following the administration of carbaryl, it has been speculated that swine produce some unique metabolite of carbaryl. However, dark urine has also been associated with carbaryl administration in rats and monkeys so a species difference in metabolism is unlikely (Hayes, 1982).

No effects were observed on groups of human volunteers consuming up to 0.06 mG/kG/day over a 6 week period; the parameters of measurment included EEG, BSP clearance, plasma and erythrocyte cholinesterase activity, hematological parameters, blood chemistry and urinalysis. Exposure to 0.12 tp 0.13 mG carbaryl/kG body weight /day over the 6 week period was associated with a slight, reversible increase in the ratio of amino acid nitrogen to creatinine in urine. This effect suggested a decreased ability of the proximal convoluted tubules of the kidney to reabsorb amino acids (Hayes, 1982).

Higher levels of human exposure to carbaryl has reportedly been associated with sweating, visual disturbances, weakness, nausia and lassitude. At higher levels of exposure as experienced in cases of poisoning, pulmonary edema occurs. Generally, patients respond positively to treatment with atropine and recovery is inconsequential (Hayes, 1982).

Skin irritation has been frequently reported in cases of accidental exposure under actual use conditions where dist levels exceed 0.75 mG/M^3 (Hayes, 1982).

Carbaryl has been reported to interfer with discrete avoidance behavior in rats and pretreatment with the microsomal enzyme inhibitor, SKF625, potentiated the response. Similar behavioral effects have been noted with other carbamate derivatives. In other studies, rats receiving 100 or 200 ppm in the diet (20 and 10 mG/kG/day, respectively) produced no consistant effects on behavioral parameters (Hayes, 1982).

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Human exposure to 2.8 mG/kG orally resulted in severe but brief poisoning. Urinary 1-naphthol levels of 18.5 ppm are associated with depressed cholinesterase activity but never systemic poisoning. This level of 1-naphthol would be excreted from a carbaryl exposure of about 39 mG/man/day or 0.55 mG/kG/day. This value is in agreement with the TLV of 5 mG/M^3 as proposed by NIOSH (1982).

Carbaryl is absorbed rapidly from the GIT. Carbaryl does cross the plancenta in rodents although less than 0.3% of the maternal dose was detected in rat fetuses 96 hours after dosing of the dams (Hayes, 1982).

Human embryonic lung cells in culture metabolize carbaryl to 1,4-naphthalendiol and N-glucuronides of 4-hydroxycarbaryl; 5,6-dihydroxy-5,6-dihydrocarbaryl; 1-naphthol; 5-hydroxycarbaryl and 1,5-naphthylenediol. Similar metabolites have been identified in human liver homogenates and the urine of human volunteers exposed to carbaryl (Hayes, 1982). These same metabolites have been identified in enzyme preparations from rabbit, rat and mouse liver and isolated from the urine of treated rabbits. Rodents also produce N-hydroxycarbayl, 1-hydroxy-5,6-dihydro-5,6-dihydroxynaphthylene. Chickens produce the same metabolites as humans plus 1,5,6-trihydroxynaphthalene and 5,6-dihydrocarbaryl. There is evidence that the metabolism of carbaryl increases during pregnancy in rodents and that some of the naphthyl ring metabolites may be sequestered by the fetus. Also, about 0.35% of the total dose of carbaryl to lactating dairy cows was recovered in milk (Hayes, 1982).

Humans excrete both naphthyl glucuronides and sulfates in urine whereas rodents excrete a cysteine conjugate of carbaryl.

The metabolism of carbaryl appears relatively similar in most mammalian species (human, rat, guinea pig, monkey, pig, rabbit and sheep). The major differences are in the amounts of the various metabolites formed: little or no hydrolysis to 1-naphthol occurs in nonhuman primates or swine compared to humans, rats or sheep. In addition to the commonly observed metabolites of carbaryl, dogs are thought to excrete a metabolite quite different to other species (Hayes, 1982).

Pipy et al (1982) demonstrated that intravenous administration of carbaryl interfered with liver ectoenzymes (i.e. serine esterases) and altered the phagocytic functions of liver Kupffer's cells. Such changes were postulated as important in the pathogenesis of liver disease and other extrahepatic functions through the inhibition of clearance of other substances that may be toxic to the animal.

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9. REPRODUCTIVE EFFECTS/TERATOGENICITY:

Tadpoles — Minor abnormalities, including fluid accumulation and lysing of yolk platelets were reported in tadpoles exposed to 1ppm carbaryl (Elliotte-Feeley, 1982)

Mouse — TD_{10} (oral) = 11660 mG/kG (day 6 to 15 of prenancy); reported fetotoxicity (NIOSH, 1982; Toxicol. Appl. Pharmacol. 51, 81 79)

TD_{10} (subcut) = 900 mG/kG (6 to 15 days of pregnancy); reported abnormalities of the central nervous system, eye/ear and muskuloskeletal system and fetotoxicity (NIOSH, 1982)

TD_{10} (subcut) = 428 mG/kG (days 6 to 14 of pregnancy); reported abnormalities of extra-embryonic structures (NIOSH, 1982)

TD_{10} (subcut) = 4176 mG/kG (days 6 to 14 of pregnancy); reported fetal deaths (NIOSH, 1982)

Abnormal sperm morphology seen in mice treated orally or ip with 1 mmol/L in drinking water (NIOSH, 1982)

Rat — TD_{10} (oral) = 2548 mG/kG (26 wk pretreatment); reported changes in the female reproductive cycle (NIOSH, 1982; Shtenberg and Rybokova, 1968)

TD_{10} (oral) = 5500 mG/kG (Multigeneration study); reported decreased fertility (refer to study for details) (NIOSH, 1982; Collins, et al, 1971)

TD_{10} (oral) = 2500 mG/kG (Multigeneration Study); reported a decrease in numbers of live births and decreased growth rate in the offspring (NIOSH, 1982;)

TD_{10} (oral) = 220 mG/kG (days 5 to 15 of pregnancy); reported decreased weaning weight of offspring (NIOSH, 1982;)

TD_{10} (oral) = 2548 G/kG (treatment of males for 26 wk); reported abnormalities in spermatogenesis (NIOSH, 1982; Shtenberg and Rybokova, 1968)

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Rabbit — TD_{10} (oral) = 1950 mG/kG (treatment days 6 to 18 of pregnancy); reported fetotoxicity and adverse effects on spermatogenesis (NIOSH, 1982; Toxicol. Appl. Pharmacol. 51, 81, 79)

TD_{10} (oral) = 2600 mG/kG (treatment days 6 to 18 of pregnancy); reported abnormalities of the body wall (NIOSH, 1982; Toxicol. Appl. Pharmacol. 51, 81, 79)

Hamster — TD_{10} (oral) = 250 mG/kG (treatment day 8 of pregnancy); reported increased fetal deaths (NIOSH, 1982; Robens, 1969)

Guinea Pig — TD_{10} (oral) = 300 mG/kG (treatment days 12 to 16 of pregnency); reported abnormalities of the muskuloskeletal system (NIOSH, 1982; Deichmann, 1973)

Gerbel — TD_{10} (oral) = 12500 mG/kG (Multigeneration Study); reported decreased fetility in females. (NIOSH, 1982; Hansen and Keeler, 1970)

TD_{10} (oral) = 20300 mG/kG (Multigeneration Study); reported decreased numbers of live births, decreased viability of the offspring and decreased fetility in females (NIOSH, 1982; Collins et al, 1971)

TD_{10} (oral) = 40600 mG/kG (Multigeneration Study); reported decreased growth rate in the offspring (NIOSH, 1982; Collins et al, 1971)

Dog — TD_{10} (oral) = 375 mG/kG (treatment days 3 to 62 of pregnancy); reported abnormalities in the craniofacial region, the body wall and the hepatobiliary system (NIOSH, 1982; Smalley et al, 1968)

TD_{10} (oral) = 750 mG/kg (treatment days 3 to 62 of pregnancy); reported decreased live births and weaning weights (NIOSH, 1982; Smalley et al, 1968)

TD_{10} (oral) = 197 mG/kG (treatment days 1 to 63 of pregnancy); reported increased post-implantation mortality and numbers of still-born (NIOSH, 1982; Deichmann, 1973)

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TD_{10} (oral) = 394 mG/kG (treatment days 1 to 63 of pregnancy); reported abnormalities of the muskuloskeltal and hepatobiliary systems (NIOSH, 1982; Deichmann, 1973)

Pig — TD_{10} (oral) = 912 mG/kG (treatment 1 to 16 weeks of pregnancy); reported increased post-implantation mortality (NIOSH, 1982; Deichmann, 1973)

The available data on the effects of carbaryl on reproduction indicate that large doses, usually associated with maternal toxicity and in many cases near the LD_{50}, are associated with reproductive effects. For the most part these effects were related to fetotoxicity, fetal deaths, post-implantation mortality, decreased litter size, and decreased postnatal performance of the young. As indicated by Hayes (1982), the studies showing reproductive effects at lower dosages were conducted in the Soviet Union and the possibility of contaminants in the carbaryl cannot be excluded.

The formations of terata was reported in guinea pigs dosed by intubation with high levels of carbaryl (Hayes, 1982) and in dogs receiving up to 375 mG carbaryl/kG body weight (Smalley et al, 1968).

Effects on spermatogenesis was reported in mice, rats, and rabbits. On the other hand, no effects were reported on the assimilation or metabolism of testosterone by the prostate gland or on the weights of the testis or sex gland in rats treated for 5 days with 34 mG/kG/day (Thomas et al, 1974) and Dieringer and Thomas, 1974). The mechanism of the possible effects of carbaryl on the male reproductive system is unclear.

10. MUTAGENICITY

Microorganisms

Induced mutations without metabolic activation in S. typhimurium @ 250 ug/plate and with metabolic activation @ 100 umol/L (NIOSH, 1982)

Mouse — Resulted in DNA inhibition in Ascites cell culture treated @ 100 umol/L (NIOSH, 1982)

Mutations were detected in a host mediated assay in mice treated @ 60 mG/kG for 5 days (NIOSH, 1982)

Hamster — Evidence of mutagenesis and unscheduled DNA synthesis was observed in Hamster fibroblasts in culture treated with 1 umol/L (NIOSH, 1982; Ahmed et al, 1977)

Adverse effects on chromosome (breaks, fragments, etc.) were reported in Hamster embryo cells in culture where donor animal were treated with 40 uG/kG (NIOSH, 1982).

Cytogenic analysis of Hamster fibroblast treated with 30 mG/L for 48 hours in culture revealed adverse effects on chromosomes (NIOSH, 1982; Ishidate and Odashima, 1977)

Human — Mitosis of human embryonic fibroblasts incubated with carbaryl was arrested in metaphase. This response was proportional to the exposure level (Vasilos et al, 1972). Similar effects were noted in HeLa cell cultures (Hayes, 1982).

Initial conventional studies indicated that carbaryl was not mutagenic (Weil et al, 1973 ; Elespuru et al, 1974) but that the nitroso derivative, nitrosocarbaryl, was mutagenic (Elespuru et al, 1974). The positive results of various test of the effects of carbaryl on the genetic system contradict these earlier findings. However, Hayes (1982) expresses the view that carbaryl would not act as a mutagen in whole animal systems because of the low absorption and rapid metabolism and excretion of the pesticide.

11. CARCINOGENICITY

Rat — TD_{10} (oral) = 5700 mG/kG/95wk - carcinogenic (NIOSH, 1982; based on Russian data----it has been suggested that the carbaryl used in these studies may have been contaminated (Hayes, 1982))

LD_{10} (implanted) = 80 mG/kG - equivocal tumorigenic agent (NIOSH, 1982; based on Russian data----refer to above comments)

The World Health Organization (Hayes, 1982) concluded that the available evidence was insufficient to evaluate the carcinogenicity of carbaryl. NIOSH classified carbaryl as an indefinite carcinogen (NIOSH, 1982). The two studies quoted above are equivocal. Carpenter (1961) did not observe an increase in neoplasia after two years treatment of rats with up to 2250 ppm in the diet. Innes et al (1969) reported no significant increase in the tumor incidence in two strains of mice that received the maximum tolerated dose of carbaryl over 18 months. Lijinski and Taylor (1977) found no significant increase in tumor incidence in rats receiving carbaryl but nitrosocarbaryl at total doses of about 177 mG/kG in males and 515 mG/kG in females was associated with carcinoma in the forestomach. Beraud (1981) demonstrated that nitrosocarbaryl accumulated in the forestomach following administration by gastric lavage. Significant accumulation was also detected in the livers. Skin tumors have also been reported in mice at the site of application of nitrosocarbaryl (Lijinski and Winter, 1981).

N-nitrosocarbaryl formation has been demonstrated in vitro in acid media and rat gastric juice (Eisenbrand, 1976). However, the occurance of such reactions under in vivo circumstances has not been demonstrated. Lijinski and Taylor (1977) studied the effects of co-administration of carbaryl and nitrite to female rats and reported no significant increase in tumor formation in the adults or their offspring exposed in utero. If the conversion of carbaryl to N-nitrosocarbaryl were demonstrated under biological conditions, the potential carcinogenicity hazard associated with carbaryl would be increased and would have to be carefully evaluated.

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APPENDIX I: DESCRIPTION OF EXPOSURE:

The following abbreviations, adopted from NIOSH (1982), were used to describe the dosage of the chemical in this toxicity profile;

TLV = Recommended concentration of a substance to which most workers can be exposed without adverse effects. The TLV can be modified by a time-weighted average (TWA is the exposure concentration for a normal 8 hour day, or 40 hour week); a short-term exposure limit (STEL is the maximum concentration to which a worker can be exposed up to 15 minutes with a maximum of 4 excursions per day with 60 minutes between excursions and provided the daily TWA is not exceeded); or as a ceiling value (CV is the maximum value for even instantaneous exposure).

TD_{lo} = Toxic Dose Low = the lowest dose of a substance introduced by any route other than inhalation over any given period of time and reported to produce any toxic effect in man or to produce carcinogenic, teratogenic, mutagenic or neoplastic effects in humans or animals.

TC_{lo} = Toxic Concentration Low = any concentration of a substance in air to which man or animals have been exposed for any given period of time and that has been reported to produce any toxic effect in man, or to produce a carcinogenic, teratogenic, mutagenic or neoplastic toxic effect in animals or humans.

LD_{lo} = Lethal Dose Low = the lowest dose of a substance, other than LD_{50}, introduced by any route other than inhalation over any given period of time and reported to have caused death in man or the lowest single dose introduced in one or more divided portions and reported to have caused death in animals.

LD_{50} = Lethal Dose Fifty = a calculated dose of a chemical substance which is expected to cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance, by any route other than inhalation, of a significant number from that population. Other lethal dose percentages, such as LD_1, LD_{10}, LD_{20}, LD_{99} etc. may also be given if available.

LC_{lo} = Lethal Concentration Low = the lowest concentration of a substance, other than an LC_{50}, in air which has been reported to have caused death in man or to have caused death in animals when they have been esposed for 24 hours or less.

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LC_{50} = Lethal Concentration Fifty = a calculated concentration of a substance in air, exposure to which for 24 hours or less would cause the death of 50% of an entire population of an experimental animal species, as determined from the exposure to the substance of a significant number from that population.

The following abbreviations were used to describe the route of administration of the substance:

Oral = administered via the mouth

Dermal = applied to the skin

ip = interperitoneally

iv = intravenously

Subcut. = injected subcutaneously

Inh = inhalation